DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

September 20, 2001

Ref: 2001-DAL-WL-37

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Rich Kruzynski
Vice President/General Manager
IV Systems
Division of Baxter Healthcare Corp.
Route 120 & Wilson Road
Round Lake, Illinois 60073

PRODUCTS: Brevibloc 2.5g added to 250mL 5% Dextrose Injection USP
Brevibloc 5.0g added to 250mL 5% Dextrose Injection USP
Cefazolin 2g added to 100mL 5% Dextrose Injection USP
Cefazolin 2g added to 100mL 0.9% Sodium Chloride Injection USP
Magnesium Sulfate 40g added to 500mL Lactated Ringers Inj. USP
Magnesium Sulfate 40g added to 1000mL Lactated Ringers Inj. USP
Magnesium Sulfate 50g added to 500mL Dextrose Injection USP
Vancomycin HCl 1g added to 250mL 5% Dextrose Injection USP
Vancomycin HCl 1g added to 250mL 0.9% Sodium Chloride Inj. USP
Sodium Citrate 4% 2000mL Dialysate Solution

Dear Mr. Kruzynski:

On July 25 - 28 and August 11, 2000, an investigator from the U.S. Food and Drug Administration's Dallas District Office completed an inspection of Baxter - COMPASS, 7525 South Freeway, Houston, Texas. The inspection disclosed that your firm receives concentrated drugs packaged in bulk which require further dilution for intravenous injection and other pharmaceutical ingredients from other manufacturers and distributors. Baxter produces, labels, and distributes to hospitals and healthcare facilities approximately [redacted] units per month of dialysate and intravenous (IV) admixture solutions. These solutions are prepared in anticipation of prescription orders and not pursuant to prescription orders from licensed practitioners for identified individual patients. This location is not licensed with the Texas State Board of Pharmacy as a pharmacy.

Section 503A

Section 127 of the FDA Modernization Act of 1997 amended the Federal Food, Drug, and Cosmetic Act (the Act) creating section 503A, *"Pharmacy Compounding."* This provision became effective on November 21, 1998, and set forth the requirements compounded products must meet to qualify for exemption from the new drug (505), certain adulteration (501(a)(2)(B)), and certain misbranding (502(f)(1)) provisions of the Act.

Section 503A contains a number of requirements that must be satisfied for compounded products to qualify for these exemptions. These include, but are not limited to, the requirement that drugs are compounded in a state licensed pharmacy and are compounded pursuant to a valid prescription for an identified individual patient.

On February 6, 2001, the United States Court of Appeals for the Ninth Circuit declared section 503A of the Act to be invalid in its entirety (Western States Medical Center v. Shalala, 238 F.3d 1090 (9th Cir. 2001)). On August 24, 2001, the United States Department of Justice appealed this decision to the U.S. Supreme Court. During the time that the appeal is pending it is FDA's position that section 503A is valid outside of the Ninth Circuit.

The drug products prepared by your firm may fall into two categories: (1) drugs manipulated within the FDA-approved labeling (such as products reconstituted according to instructions provided in the FDA-approved labeling) and (2) drugs not manipulated within the FDA-approved labeling (such as dialysate products).

Drugs manipulated within the FDA-approved labeling

Section 503A of the Act excludes from the definition of compounding "the mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling." As articulated in the language of the House-Senate Conference Report on section 503A (H. Rept. 105-399 (1997)), "nothing in this provision is intended to change or otherwise affect the Act with respect to reconstitution or other similar processing that is done pursuant to a manufacturer's approved labeling, and other directions from such manufacturer consistent with that labeling. In general, such practices, as performed by a licensed practitioner for an identified individual patient, are appropriately regulated by state boards of pharmacy. The conferees intend that facilities required to register with the FDA, including those which are engaged in non-patient specific compounding and reconstitution activities are appropriately regulated under the Federal Food, Drug, and Cosmetic Act."

Antibiotic premixes reconstituted pursuant to the manufacturer's approved labeling, are, therefore, excluded from the definition of compounding in section 503A and are subject to all applicable sections of the Act. It has been FDA's position that reconstitution and manipulation within the scope of the FDA-approved labeling satisfies the requirements of sections 505 and 502(f)(1), and such operation is subject to the requirements of section 501(a)(2)(B).

A review of the products prepared by your firm, including antibiotic premixes, indicates that your drugs are not manipulated within their FDA-approved labeling (see below).

Drugs not manipulated within the FDA-approved labeling
Products prepared by your firm that are not manipulated within FDA-approved labeling (such as the dialysate solutions), require either approved applications or conformance with the requirements of section 503A to qualify for the exemptions from the Act.

The antibiotic premixes reconstituted by your firm are not manipulated within the FDA-approved labeling. The antibiotic premixes are assigned expiration dates outside of those in the FDA-approved labeling. For example, your firm reconstitutes Vancomycin HCl 1 gram with 5% Dextrose for Injection. The FDA-approved labeling states that after reconstitution and dilution with 5% Dextrose, the product may be stored for 14 days under refrigeration. Your firm assigns a 30-day expiration date. Because the antibiotic premixes manipulated by your firm are outside the FDA-approved labeling, these products require either approved applications and must comply with section 501(a)(2)(B) and 502(f)(1), or must conform to the requirements of section 503A to qualify for the exemptions from the Act.

Because the Houston facility is not a state licensed pharmacy, your firm can not qualify for the exemptions provided by section 503A and is subject to all applicable requirements of the Act, including sections 501(a)(2)(B), 502(f)(1) and 505.

Unapproved New Drugs
Your drug products:

- Brevibloc 2.5g added to 250mL 5% Dextrose Injection USP
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- Cefazolin 2g added to 100mL 5% Dextrose Injection USP
- Cefazolin 2g added to 100mL 0.9% Sodium Chloride Injection USP
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- Magnesium Sulfate 50g added to 500mL Dextrose Injection USP
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- Vancomycin HCl 1g added to 250mL 0.9% Sodium Chloride Inj. USP
- Sodium Citrate 4% 2000mL Dialysate Solution

are drugs within the meaning of section 201(g) of the Act which may not be introduced or delivered for introduction into interstate commerce under section 505(a) of the Act, since they are new drugs within the meaning of section 201(p) of the Act and no approval of an application filed pursuant to section 505(b) is effective for such drugs.

Misbranding
Furthermore, the drug products listed above are misbranded in that their labeling fails to bear adequate directions for use for which the articles are represented or suggested and they are not exempt from this requirement under Title 21 Code of Federal Regulations (CFR) Part 201.115, since the articles are new drugs within the meaning of section 201(p) and no approved applications filed pursuant to section 505(b) are effective for these drugs.

Current Good Manufacturing Practices
The inspection also revealed significant violations of the Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMP) 21 CFR 210 and 211.

A Form FDA-483 (Inspectional Observations) was issued to and discussed with Mr. James Reynolds, Director of Operations, in the presence of Mr. Richard Dillow, Center Manager, at the completion of the inspection. I have enclosed a copy of the FDA-483 for your information. The violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held in conformance with CGMP. Failure to comply with CGMP constitutes a failure to comply with the requirements of the Act.

The violations include but may not be limited to the following:

1. Failure to determine that each batch of drug product conforms to final specifications, including the identity and strength of each active ingredient, prior to product release [21 CFR 211.165(a)].

2. Failure to retain reserve samples of drug products [21 CFR 211.170(b)].

3. Failure to have written procedures describing in sufficient detail the handling and approval or rejection of components and drug product containers [21 CFR 211.80(a)].

We have reviewed your response to the FDA-483 dated August 17, 2000, and believe that you have not adequately addressed all of the issues. Your response contends that because your firm uses only commercially approved products in your finished drug products, there are no requirements either for testing the final product and incoming component or to have written procedures describing in sufficient detail the handling, sampling, testing, and approval or rejection of components and drug product containers. We do not agree. As a drug product manufacturer, you are required to follow the regulations in the Current Good Manufacturing Practices (21 CFR Parts 210 and 211). These regulations require manufac-

turers to test components and finished products. With respect to the testing of components, we will use enforcement discretion. While the CGMPs specifically require testing of components, the use of commercially available finished products mitigates the concern in this area. You should have in place adequate procedures to ensure properly identified raw materials are received and used in production (see item 3 in the list of CGMP violations). However, you must test your finished products in accordance with written procedures to assure conformity with their specifications.

We acknowledge the Houston Corrective Action Plan, provided to the investigator during the inspection as a means of responding to inspectional findings. You reported that a review was made of a prior 30 days of batch production records. You indicated that Baxter's review and evaluation of these records determined that all products had been prepared correctly. The record review by our investigator determined that several records failed to have documentation supporting the performance of significant manufacturing steps by specific employees. The investigator also established that several of the records showed blank entries, inaccurate information, and were lacking the names or initials of key personnel reviewing and approving the records for batch acceptance and release. We do not believe that your after-the-fact review of these production documents can provide the support needed by Baxter to verify drug product quality and purity.

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that all drug products manufactured and processed at all Baxter – COMPASS facilities are in compliance with federal laws and regulations. Your failure to promptly correct these violations and prevent future violations may result in regulatory action without further notice such as seizure and/or injunction.

Please notify this office within 15 working days of receipt of this letter of the specific steps you have taken to correct these violations, including an explanation of each step being taken to prevent the recurrence of the violations.

You should address your reply to this letter to the U.S. Food and Drug Administration, Attention: Jim Lahar, Compliance Officer, at the above address.

Sincerely,

Michael A. Chappell
Director, Dallas District

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